Constipation Agents

EOCCO POLICY

Policy Type: PA Pharmacy Coverage Policy: EOCCO144

Description

These medications have different mechanisms of action targeting tissues in the gastrointestinal tract to either increase intestinal fluid secretion, increase colon motility, and/or increase colon transit time.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
generic prucalopride	Chronic idiopathic constipation	1 mg tablets	30 tablets/30 days
		2 mg tablets	30 tablets/30 days
prucalopride (Motegrity)	Chronic idiopathic constipation	1 mg tablets	30 tablets/30 days
		2 mg tablets	30 tablets/30 days
plecanatide (Trulance)	Chronic idiopathic constipation Irritable bowel syndrome, with constipation	3 mg tablets	30 tablets/30 days
linaclotide (Linzess)	Chronic idiopathic constipation Functional constipation	72 mcg capsules	30 capsules/30 days
	Chronic idiopathic constipation	145 mcg capsules	30 capsules/30 days
	Irritable bowel syndrome, with constipation	290 mcg capsules	30 capsules/30 days
Generic lubiprostone, Amitiza	Irritable bowel syndrome, with constipation	8 mcg capsules	60 capsules/30 days
	Chronic idiopathic constipation Opioid-induced constipation, chronic non-cancer pain	24 mcg capsules	60 capsules/30 days
methylnaltrexone bromide (Relistor)	Opioid-induced constipation, chronic non-cancer pain Opioid-induced constipation with advanced illness or pain caused by active cancer requiring opioid dosage escalation	150 mg tablets	90 tablets/30 days
		12 mg vial/syringe	30 single use vials or syringes/30 days
		8 mg vial/syringe	30 single use vials or syringes/30 days
naldemedine (Symproic)	Opioid-induced constipation, chronic non-cancer pain	0.2 mg tablets	30 tablets/30 days
		12.5 mg tablets	30 tablets/30 days

naloxegol (Movantik)		25 mg tablets	30 tablets/30 days

Initial Evaluation

** Prucalopride (Motegrity), plecanatide (Trulance), linaclotide (Linzess), lubiprostone (Amitiza), methylnaltrexone bromide (Relistor), naldemedine (Symproic), and naloxegol (Movantik) are medications used to treat constipation, a non-funded condition according to the Oregon Health Plan Prioritized List of Healthcare Services.

Opioid induced constipation falls under a non-covered line; however, treatment with opioids for chronic pain under a covered line allows for these therapies to be covered. Examples of covered lines that require chronic opioids include conditions of the back and spine, a covered cancer diagnosis, fractures, etc.

If the condition is a covered line according to the Oregon Health Plan Prioritized List of Healthcare Services **OR** the condition is *not* a covered line, but the member has a comorbid condition that would be improved if the non-covered indication is treated, the following applies:

I. **Prucalopride (Motegrity), plecanatide (Trulance), linaclotide (Linzess), lubiprostone (Amitiza), Methylnaltrexone bromide (Relistor), naldemedine (Symproic),** and **naloxegol (Movantik)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **OR**
      1. Member is 6 years of age or older if prescribed (linaclotide) Linzess**; AND**
   B. Treatment with the following has been ineffective, contraindicated, or not tolerated:
      1. Two different types of agents from the following OTC laxatives:
         i. Stool softener (e.g. docusate sodium); **OR**
         ii. Osmotic agent (e.g. polyethylene glycol); **OR**
         iii. Stimulant laxative (e.g. sennoside); **OR**
         iv. Other; **AND**
   C. A diagnosis of one of the following:
      1. **Opioid-Induced Constipation (OIC)**; **AND**
         i. The request is for generic lubiprostone; **OR**
         ii. The request is for methylnaltrexone bromide (Relistor), naldemedine (Symproic), naloxegol (Movantik), linaclotide (Linzess), or Brand Amitiza; **AND**
            a. Treatment with generic lubiprostone has been ineffective, contraindicated, or not tolerated; **OR**
      2. **Chronic Idiopathic Constipation (CIC); AND**
         i. The request is for generic lubiprostone; **OR**

ii. The request is for generic prucalopride, plecanatide (Trulance), linaclotide (Linzess), or Brand Amitiza; **AND**
   a. Treatment with generic lubiprostone has been ineffective, contraindicated, or not tolerated; **OR**
iii. The request is for prucalopride (Motegrity); **AND**
   a. Treatment with generic prucalopride has been ineffective, contraindicated, or not tolerated; **AND**
   b. Treatment with generic lubiprostone has been ineffective, contraindicated, or not tolerated; **OR**

3. **Irritable Bowel Syndrome with Constipation (IBS-C); AND**
   i. The request is for generic lubiprostone; **OR**
      a. The request is for Brand Amitiza; **AND**
         i. Treatment with generic lubiprostone has been ineffective, contraindicated, or not tolerated; **OR**
   ii. The request is for plecanatide (Trulance), linaclotide (Linzess); **AND**
      a. Treatment with generic lubiprostone has been ineffective, contraindicated, or not tolerated; **OR**
      b. The member is male; **OR**
4. **Functional Constipation (FC); AND**
   i. The request is for linaclotide (Linzess); **AND**
      a. Member is 6-17 years of age

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise; **AND**
III. Member has an improvement in disease symptoms (e.g., improvement in bowel movements or abdominal pain)

Supporting Evidence

I. The safety and efficacy of these agents have not been established in pediatric patients.
II. Overall, guidelines support the use of OTC laxatives as the primary approach to constipation. It is widely used in clinical practice based on their ease of accessibility with few safety concerns.
   - The American Gastroenterological Association (AGA) guidelines on OIC provides a strong recommendation for the use of OTC laxatives as a first line agent for OIC based on moderate quality evidence. The panel favored use of a combination of at least 2 types of laxatives before escalating therapy.

- The joint American Gastroenterological Association (AGA) and American College of Gastroenterology (ACG) guidelines on CIC recommends the use of OTC laxatives as first line therapy for CIC, particularly with a strong recommendation for polyethylene glycol and bisacodyl.
- The American Gastroenterological Association (AGA) guidelines on IBS-C recommends the use of PEG for IBS-C based on a conditional recommendation. PEG is widely available with few side effects compared with other osmotic laxatives. PEG has been shown to improve constipation but not abdominal pain. The Canadian Association of Gastroenterology guidelines recommends offering IBS patients with psyllium supplementation to help improve IBS symptoms.

III. Generic lubiprostone is a preferred step alternative following use of OTC laxatives and trial and failure is required prior to coverage of non-preferred agents.

IV. Lubiprostone (Amitiza) is FDA approved for OIC in adults. The efficacy of lubiprostone (Amitiza) in OIC has been confirmed in at least 3 RCTs. In the Cryer et al study, the investigators compared lubiprostone 24 mcg to placebo twice daily for 12 weeks. The primary endpoint was change from baseline in spontaneous bowel movements (SBM) frequency, defined as < 3 SBMs per week at baseline. The change in SBM frequency was higher in the lubiprostone group at week 8 (P=0.005). These findings were confirmed with the Jamal et al study which found a statistically greater increase in SBM frequency with lubiprostone vs placebo (3.2 vs. 2.4, respectively; P=0.001). The most common adverse effects noted were nausea, diarrhea, and abdominal distention. The efficacy in patients on methadone remains uncertain as most patients in the studies were on non-methadone therapy. Although AGA guidelines do not currently provide a recommendation for lubiprostone in OIC, the Multinational Association for Supportive Care in Cancer (MASCC) suggests lubiprostone as an appropriate alternative following conventional laxatives.

- Although used off-label, use of linaclotide (Linzess) in the OIC setting is supported by MASCC guidelines and a phase II RCT demonstrating a statistically significant improvement in SBMs/week. The mean changes from baseline in SBMs/week during the treatment period were 2.9 and 3.5 in the linaclotide 145 and 290 mcg groups respectively (P < 0.01 for both doses) vs 1.6 in the placebo group. The most common adverse effect was diarrhea and was generally mild.

V. Lubiprostone (Amitiza) is FDA approved for CIC in adults. The joint AGA and ACG guidelines suggest the use of lubiprostone for CIC in adults who do not respond to OTC agents (conditional recommendation). This is based on three 4-week RCTs comparing lubiprostone and placebo. The pooled data showed that lubiprostone resulted in an increased number of SBMs per week compared with placebo (MD 1.98, 95% CI 1.17-2.79).

VI. Lubiprostone (Amitiza) is FDA approved for IBS-C in adult women. The AGA suggests using lubiprostone in patients with IBS-C (conditional recommendation). This is based on 2 identically designed RCTs that included 1154 patients with IBS-C. Lubiprostone was superior to placebo for

a modified FDA response (i.e., adequate abdominal pain and SBM response RR 0.88, 95% CI 0.79-0.96). Data from a long-term safety study in patients with IBS-C found lubiprostone to be well tolerated. The FDA approval for IBS-C is limited to women 18 years or older as the majority of patients in the clinical trials were women.

VII. Functional constipation is a diagnosis of exclusion defined by the Rome IV Diagnostic Criteria for Functional Constipation. This is characterized by symptoms of infrequent, hard, and/or large stools, fecal incontinence, painful defecation, or stool retention that is not explained by another medical condition. Functional constipation is responsible for more than 95% of constipation in pediatrics.

VIII. The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) 2014 guidelines on functional constipation recommend PEG as a first line therapy for children presenting with fecal impaction and as maintenance therapy. Other appropriate alternatives include lactulose, milk of magnesia, mineral oil, and other stimulant laxatives if PEG is not available.

IX. Linaclotide (Linzess) is FDA approved for functional constipation (FC) in children ages 6-17. The approval was based on a double-blind RCT studying linaclotide in children ages 6-17 years old. A significant improvement in 12-week spontaneous bowel movement (SBM) frequency rate and stool consistency was observed in patients treated with linaclotide compared with those receiving placebo. The most reported adverse effect was diarrhea.

References

1. Trulance [Prescribing Information]. New York, NY: Synergy Pharmaceuticals, Inc. January 2017.
2. Motegrity [Prescribing Information]. Lexington, MA: Shire US, Inc. December 2018.
3. Linzess [Prescribing Information]. North Chicago, IL: Abbvie and Ironwood Pharmaceuticals, Inc. June 2023.
4. Amitiza [Prescribing Information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc. November 2020.
5. Relistor [Prescribing Information]. Bridgewater, NJ: Salix Pharmaceuticals, Inc. November 2018.
6. Movantik [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals. May 2019.
7. Symproic [Prescribing Information]. Raleigh, NC: BioDelivery Sciences International, Inc. April 2019.
8. Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S. American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation. *Gastroenterology*. 2019;156(1):218-226.
9. Chang L, Chey WD, Imdad A, et al. American Gastroenterological Association-American College of Gastroenterology Clinical Practice Guideline: Pharmacological Management of Chronic Idiopathic Constipation. Am J Gastroenterol. 2023;118(6):936-954. doi:10.14309/ajg.0000000000002227 Jun;164(7):1086-1106. doi: 10.1053/j.gastro.2023.03.214. PMID: 37211380.
10. Chang L, Sultan S, Lembo A, Verne GN, Smalley W, Heidelbaugh JJ. AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome With Constipation. Gastroenterology. 2022;163(1):118-136. doi:10.1053/j.gastro.2022.04.016
11. Cryer B, Katz S, Vallejo R, Popescu A, Ueno R. A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. Pain Med. 2014;15(11):1825-1834. doi:10.1111/pme.12437

12. Jamal MM, Adams AB, Jansen JP, Webster LR. A randomized, placebo-controlled trial of lubiprostone for opioid-induced constipation in chronic noncancer pain. Am J Gastroenterol. 2015;110(5):725-732. doi:10.1038/ajg.2015.106
13. Spierings ELH, Drossman DA, Cryer B, et al. Efficacy and Safety of Lubiprostone in Patients with Opioid-Induced Constipation: Phase 3 Study Results and Pooled Analysis of the Effect of Concomitant Methadone Use on Clinical Outcomes. Pain Med. 2018;19(6):1184-1194. doi:10.1093/pm/pnx156
14. Davies A, Leach C, Caponero R, et al. MASCC recommendations on the management of constipation in patients with advanced cancer. Support Care Cancer. 2020;28(1):23-33. doi:10.1007/s00520-019-05016-4
15. Moayyedi P, Andrews CN, MacQueen G, et al. Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Irritable Bowel Syndrome (IBS). J Can Assoc Gastroenterol. 2019;2(1):6-29. doi:10.1093/jcag/gwy071
16. Tabbers MM et al. Evaluation and Treatment of Functional Constipation in Infants and Children: Evidence-Based Recommendations From ESPGHAN and NASPGHAN. *Journal of Pediatric Gastroenterology and Nutrition*. 2014;58: 258-274. Accessed July 18, 2023. Thomson (naspghan.org)
17. Allergan. Linaclotide Safety and Efficacy in Pediatric Participants, 6 to 17 Years of Age, With Irritable Bowel Syndrome With Constipation (IBS-C) or Functional Constipation (FC). Clinicaltrials.gov. July 19, 2019. Updated June 29, 2023. Accessed July 7, 2023. Study Record | Beta ClinicalTrials.gov
18. Brenner DM, Argoff CE, Fox SM, et al. Efficacy and safety of linaclotide for opioid-induced constipation in patients with chronic noncancer pain syndromes from a phase 2 randomized study. Pain. 2020;161(5):1027-1036. doi:10.1097/j.pain.0000000000001754Title

Policy Implementation/Update:

Action and Summary of Changes	Date
Added generic prucalopride to the policy and had it step through preferred agents	01/2025
Added expanded indication of Linzess in functional constipation for children ages 6-17 years old. Added pathway to coverage for Linzess for off-label use in OIC.	09/2023
Policy updated to include all constipation agents for OIC, CIC, and IBS-C, requiring trial and failure of two OTC laxatives followed by a step through the preferred agent, generic lubiprostone.	06/2023
Transitioned criteria to policy: removed required trial and failure of lubiprostone (Amitiza) for all agents	11/2019
Previous reviews	03/2018
Criteria created	01/2018